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BRIEF REPORT

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Bone mineral density and the risk of incident dementia: A meta-analysis

Christine W. Lary PhD[1,2] | Samuel Ghatan BS[3] | Meghan Gerety MS[4] | Alexandra Hinton MPH[2] | Archana Nagarajan BS[1,2,5] | Clifford Rosen MD[2] | Ryan D. Ross PhD[6] | David A. Bennett MD[7] | Anita L. DeStefano PhD[8] | Mohammad A. Ikram MD, PhD[3] | Fernando Rivadeneira MD, PhD[3] | Douglas P. Kiel MD[9,10] | Sudha Seshadri MD[11,12] | Alexa Beiser PhD[8,12]

[1]Roux Institute at Northeastern University, Portland, Maine, USA

[2]MaineHealth Institute for Research, Scarborough, Maine, USA

[3]Erasmus Medical Center, Rotterdam, The Netherlands

[4]University of Pennsylvania, Philadelphia, Pennsylvania, USA

[5]Tufts University Graduate School of Biomedical Sciences, Boston, Massachusetts, USA

[6]Department of Anatomy & Cell Biology, Rush University Medical Center, Chicago, Illinois, USA

[7]Rush Alzheimer's Disease Center, Rush University Medical Center, Chicago, Illinois, USA

[8]Boston University School of Public Health, Boston, Massachusetts, USA

[9]Hinda and Arthur Marcus Institute for Aging Research, Hebrew SeniorLife, Boston, Massachusetts, USA

[10]Department of Medicine, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, Massachusetts, USA

[11]Glenn Biggs Institute for Alzheimer's & Neurodegenerative Diseases, UT Health, San Antonio, Texas, USA

[12]Boston University School of Medicine, Boston, Massachusetts, USA

Correspondence
Christine W. Lary, Roux Institute at Northeastern University, Portland, ME 04101, USA.
Email: c.lary@northeastern.edu

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Abstract

Background: It is not known whether bone mineral density (BMD) measured at baseline or as the rate of decline prior to baseline (prior bone loss) is a stronger predictor of incident dementia or Alzheimer's disease (AD).

Methods: We performed a meta-analysis of three longitudinal studies, the Framingham Heart Study (FHS), the Rotterdam Study (RS), and the Rush Memory and Aging Project (MAP), modeling the time to diagnosis of dementia as a function of BMD measures accounting for covariates. We included individuals with one or two BMD assessments, aged ≥60 years, and free of dementia at baseline with follow-up available. BMD was measured at the hip femoral neck using dual-energy X-ray absorptiometry (DXA), or at the heel calcaneus using quantitative ultrasound to calculate estimated BMD (eBMD). BMD at study baseline ("baseline BMD") and annualized percentage change in BMD

This manuscript is dedicated to Carmen Khoo, 1993–2022, who performed the most recent analysis in Framingham for this study before her untimely death. She was a great scientist, colleague, and friend, and will be sorely missed. Thank you, Carmen, for your contributions; you live on in all of us.

prior to baseline ("prior bone loss") were included as continuous measures. The primary outcome was incident dementia diagnosis within 10 years of baseline, and incident AD was a secondary outcome. Baseline covariates included age, sex, body mass index, ApoE4 genotype, and education.

Results: The combined sample size across all three studies was 4431 with 606 incident dementia diagnoses, 498 of which were AD. A meta-analysis of baseline BMD across three studies showed higher BMD to have a significant protective association with incident dementia with a hazard ratio of 0.47 (95% CI: 0.23–0.96; $p = 0.038$) per increase in g/cm^2, or 0.91 (95% CI: 0.84–0.995) per standard deviation increase. We observed a significant association between prior bone loss and incident dementia with a hazard ratio of 1.30 (95% CI: 1.12–1.51; $p < 0.001$) per percent increase in prior bone loss only in the FHS cohort.

Conclusions: Baseline BMD but not prior bone loss was associated with incident dementia in a meta-analysis across three studies.

KEYWORDS

Alzheimer's disease, bone loss, BMD, dementia, osteoporosis

INTRODUCTION

The association between bone mineral density (BMD) and dementia has been found in many studies.[1–7] It may be due to common risk factors that include age, lifestyle factors including lack of physical activity and smoking, vitamin D deficiency, and ApoE4 genotype,[8] and common mechanisms such as estrogen signaling, inflammation, brain-derived molecules affecting bone, and bone-derived mediators affecting the brain.[9] Low BMD has been associated with time to Alzheimer's disease (AD) in a Chinese cohort study,[1] and with both time to AD and all-cause dementia in the Framingham Heart Study (FHS) in women, but not men.[2] Low BMD was also associated with brain structural changes and cognitive performance in FHS.[3] Two large US-based prospective studies found women with more rapid bone loss were more likely to develop cognitive decline.[4,5] More recently, a large Canadian-based cohort study found a significant association between cognitive decline and bone loss that was strongest in women,[6] and a large prospective study from Hong Kong showed low BMD at multiple skeletal sites to be associated with incident dementia.[7]

Thus, the associations between baseline BMD and incident dementia, and prior bone loss and cognitive decline, are established.[1,2,4,5,7] However, the association between prior bone loss and incident dementia has not yet been studied. Furthermore, baseline BMD and prior bone loss have not been directly compared for association with incident dementia in the same study. We hypothesize that prior bone loss, representing the prior rate of bone loss over time, may show a stronger association with incident dementia than BMD measured at a single time point. Thus, we sought to compare the size (effect estimate) and strength (p-value) of the association between BMD and prior bone loss with incident

Key points

- There is a significant protective association between higher baseline bone mineral density (BMD) and time to dementia when meta-analyzing across three studies with 4431 participants.
- The association between prior bone loss and incident dementia was only significant in one study and not in the meta-analysis.
- The protective association of baseline BMD with incident dementia is robust to skeletal site and to participant characteristics such as age and sex, which varied across studies.

Why does this paper matter?

It is important to know whether baseline bone density or prior bone loss is a better predictor of future dementia risk when considering each as a potential biomarker and when examining potential pathological mechanisms connecting bone loss and cognitive decline.

dementia in analyses in three different studies and a meta-analysis of each measure across studies.

METHODS

Cohorts

The FHS is an ongoing three-generation community-based study initiated in 1948 with enrollment into the ancillary Framingham Osteoporosis Study beginning in 1991.[10] We included the Original cohort (BMD assessments at exams 20 [1986–1990] and 24 [1995–1998]) and the Offspring cohort (BMD assessments at the exam 6 [1995–1998] and exam 8 [2005–2008] call-back visits). The Rotterdam Study (RS) is an ongoing prospective population-based cohort started in 1990[11] with members of the RS1 cohort included with BMD assessments at visits 2 (1993–1995) and 3 (1997–1999). The Rush Memory and Aging Project (MAP)[12] was started in 1997 by the Rush Alzheimer's Disease Center (RADC) as a longitudinal cohort study which recruits older participants without known dementia.

Exposures and covariates

In FHS and RS, BMD of the hip femoral neck was measured using dual-energy X-ray absorptiometry (DXA) in g/cm^2 (GE Lunar Prodigy, coefficient of variation 1.7%[10] in FHS and 3.2%[13] in RS) with roughly 4 or 8 years between BMD measurements for RS and FHS, respectively. In MAP, Quantitative Ultrasound (QUS) with the Hologic Sahara measured broadband ultrasound attenuation (BUA) and speed of sound (SOS) in the mid calcaneus to estimate heel BMD in g/cm^2 as per the manufacturer's software with a precision of 0.014 g/cm^2. Dementia follow-up began after the second ("baseline") BMD assessment for FHS and RS or the only assessment for MAP (Figure 1). Baseline BMD and prior bone loss (annualized percentage decline from the first BMD measure) were the primary exposure variables. We considered the following covariates based on evidence of a confounding between BMD and dementia[8]: age, sex, current smoking, current estrogen usage in women, body mass index (BMI), educational attainment categorized as high school or less or some college or more, and ApoE4 status given by one or two copies of the APOE ε4 allele. Activity level is also a potential confounder but was not included due to lack of consistent measurement across studies. Covariates that did not show a significant association with dementia in FHS were not included, and the final models included age, sex, ApoE4 status, BMI, and education. Participants who were ≥ 60 years at study baseline, had one (MAP) or two (FHS, RS) BMD assessments, were free of dementia, and had dementia follow-up available were included (Figure S1 for details).

Outcomes

The primary outcome was incident dementia, and the secondary outcome was incident AD. The surveillance methods and dementia tracking for FHS are published.[14] Diagnoses were made by a panel with a neurologist and a neuropsychologist following referrals or decline in cognitive status.[14] In RS, cognitive testing[15] was used for referral to a neurologist-led adjudication panel. In MAP, annual cognitive testing with a global cognition summary measure and individual domains and diagnosis of cognitive impairment were performed at home visits, and a decision tree informed clinical diagnoses by combining data reduction techniques for the cognitive performance testing with a series of discrete clinical judgments made in series by a neuropsychologist and a clinician, and the clinician is then asked to confirm the decisions.[12,16] In FHS and RS we noted dementia and AD diagnoses up to 10 years after the baseline visit. In MAP, diagnoses were made at annual visits, and so we included diagnoses within 10 annual visits of the baseline visit.

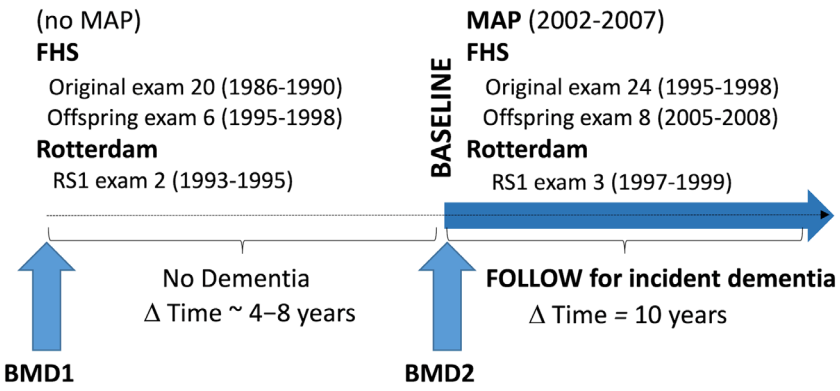

FIGURE 1 Study design. Bone mineral density (BMD) of the hip femoral neck or heel calcaneus was collected at one or two timepoints with the second (Framingham Heart Study, Rotterdam Study) or only (Memory and Aging Project) timepoint serving as study baseline. Participants were ≥60 and free of dementia at baseline and followed for 10 years for incident dementia or Alzheimer's disease. The time between BMD measurements was roughly 4 years for the Rotterdam Study and 8 years for the Framingham Heart Study.

Statistical methods

We used Cox proportional hazards model to examine the associations between baseline BMD in g/cm^2 or prior bone loss in percent per year and incident dementia or AD adjusting for covariates and family structure in FHS as a random effect, where we computed a kinship matrix from the pedigree file using the kinship2 package in R.[17] We tested the proportional hazards assumption and inspected the Martingale residuals in each model. We performed a meta-analysis of baseline BMD across all three studies and prior bone loss in FHS and RS using fixed and random effects models with the inverse variance method to pool results, testing for study heterogeneity in models with at least three studies using Cochran's Q test. We performed power calculations using the "powerSurvEpi" package in R and showed 82% power for baseline BMD across the three studies and >99% power for prior bone loss across FHS and RS. For all analyses we used a Type I error rate of 5%.

RESULTS

The characteristics of the participants are shown in Table 1. The sample size, female proportion, and median age at baseline were 1643, 57%, and 73 years in FHS; 2138, 56%, and 72 years in RS; and 650, 74%, and 81 in MAP. The median baseline BMD and prior bone loss were 0.85 g/cm^2 and 0.22% per year, respectively, in FHS, and 0.87 g/cm^2 and 0.09%, respectively, in RS. In MAP the median baseline estimated BMD (eBMD) was 0.43 g/cm^2. The number of dementia diagnoses in FHS, RS, and MAP, respectively, were 207 (13%), 210 (10%), and 189 (29%), and for AD, 167 (10%), 152 (7%), and 179 (28%).

We did not observe significant associations between baseline BMD and incident dementia in any of the individual studies (Table 2). The meta-analysis across studies revealed a significant association between baseline BMD and incident dementia with HR = 0.47 per increase in g/cm^2 (95% CI: 0.23–0.96; $p = 0.038$), or HR = 0.91 per standard deviation (SD) increase (95% CI: 0.84–0.995), with no evidence of heterogeneity ($p = 0.74$) and a significant association with AD (HR = 0.48 per increase in g/cm^2; 95% CI: 0.24–0.98; $p = 0.043$; or HR = 0.92 per SD increase; 95% CI: 0.84–0.998) with no evidence of heterogeneity ($p = 0.73$). We observed a significant association between prior bone loss and incident dementia in FHS (HR = 1.30; 95% CI: 1.12–1.51; $p < 0.001$) but not in RS (Table 2) or in the meta-analysis estimate from FHS and RS.

DISCUSSION

We modeled time to dementia or AD in a set of dementia-free adults from FHS, RS, and MAP, as a function of baseline BMD (of the hip femoral neck or heel calcaneus) or annualized decline in BMD prior to baseline (prior bone loss). We showed a significant protective association between higher baseline BMD and

Characteristic	FHS, $N = 1643$[a]	RS, $N = 2138$[a]	MAP, $N = 650$[a]
Female sex	944 (57%)	1201 (56%)	481 (74%)
Age at baseline visit (years)	73 (66, 79)	72 (67, 77)	81 (77, 85)
Prior bone loss (% per year)[b]	0.22 (−0.30, 0.78)	0.09 (−0.69, 0.93)	–
Baseline BMD (g/cm^2)	0.85 (0.75, 0.96)	0.87 (0.77, 0.96)	0.43 (0.34, 0.52)
Current smoker[c]	101 (6.2%)	318 (14.8%)	23 (3.5%)
BMI at baseline visit[c]	27.1 (24.4, 30.4)	26.5 (24.3, 29.1)	26.5 (23.7, 29.8)
≥1 APOE ε4 allele	338 (21%)	599 (28%)	143 (22%)
Missing	19 (1.2%)	0 (0%)	<11 (<1%)
Highest level of education			
College	788 (48%)	198 (9%)	445 (68%)
HS	557 (34%)	1610 (75%)	205 (32%)
Missing	298 (18%)	0 (0%)	0 (0%)
Incident dementia by year 10	207 (13%)	210 (10%)	189 (29%)
Incident AD by year 10	167 (10%)	152 (7%)	179 (28%)

[a]Number (%); median (interquartile range).
[b]Prior bone loss not available.
[c]<11 missing.

TABLE 1 Framingham Heart Study (FHS), Rotterdam Study (RS), and Memory and Aging Project (MAP) cohort characteristics.

TABLE 2 Comparison and meta-analysis of the association between bone mineral density (BMD) (g/cm^2) or prior bone loss (% change per year) and incident dementia or incident Alzheimer's disease (AD) across studies. Each measure is included as a continuous measure adjusting for age, sex, ApoE4 status, education, and body mass index (BMI). The model is described by the main predictor and the outcome in the first column. Hazard ratio, 95% confidence interval, and *p*-value are given for individual studies, and the results of the common effect and random effect meta-analyses are given.

Outcome	Predictor	Study	Study results[a]
Dementia	BMD (g/cm^2)	FHS	0.47 (0.13–1.69, $p = 0.250$)
		RS	0.64 (0.21–1.97, $p = 0.437$)
		MAP	0.33 (0.09–1.16, $p = 0.084$)
		Meta (Fixed)	0.47 (0.23–0.96, $p = 0.038$)
		Meta (Random)	0.47 (0.23–0.96, $p = 0.038$)
AD	BMD (g/cm^2)	FHS	0.59 (0.15–2.38, $p = 0.460$)
		RS	0.68 (0.18–2.6, $p = 0.57$)
		MAP	0.34 (0.091, 1.23, $p = 0.10$)
		Meta (Fixed)	0.48 (0.24–0.98, $p = 0.043$)
		Meta (Random)	0.48 (0.24–0.98, $p = 0.043$)
Dementia	Prior bone loss (% per year)	FHS	1.30 (1.12–1.51, $p < 0.001$)
		RS	0.99 (0.92–1.07, $p = 0.837$)
		Meta (Fixed)	1.05 (0.98–1.12, $p = 0.17$)
		Meta (Random)	1.12 (0.87–1.47, $p = 0.38$)

[a]Hazard Ratio (95% confidence interval, *p*-value).

time to dementia and time to AD when meta-analyzing across three studies, but we found a significant association between prior bone loss and incident dementia in only one study. Our study is the first to measure the association between prior bone loss and incident dementia and to compare the association between baseline BMD and prior bone loss with incident dementia in the same study. Our positive results for baseline BMD and dementia are consistent with prior studies,[1,2,7] and while our results for bone loss and dementia do not have precedent, other studies have shown a significant association between bone loss and cognitive decline.[4,5]

While we have adjusted by known confounders, we did not adjust for activity level which was not consistently measured across studies, so part of the association may be due to confounding by activity level. We note that the average BMD was roughly the same in FHS and RS (0.85 and 0.87 g/cm^2, respectively), but was only 0.43 g/cm^2 in MAP for eBMD. Part of this difference may be the higher median age (81 in MAP and 73 and 72 in FHS, RS, respectively) and higher percentage of females (74% in MAP and 57% and 56% in FHS, RS, respectively), as both are associated with lower BMD. Also, in MAP, BMD was measured at the heel via ultrasound and in FHS and RS at the femoral neck via DXA. The correlation of heel eBMD with BMD at other skeletal sites has been shown to be significant but modest,[18] although eBMD does show strong heritability like other skeletal sites,[19] and has moderate sensitivity and high specificity in detecting osteoporosis compared to hip and spine via DXA.[20]

We only found a significant association between prior bone loss and incident dementia in FHS, not RS. We note that the average rate of prior bone in FHS was greater than that of RS (0.22 vs. 0.09%/year, respectively), although both estimates showed high variability. Also, RS had a a shorter interval between bone density measures than FHS (4 compared with 8 years). Longer bone loss assessment allows for greater precision, which is important considering the high variability in bone loss overall. Thus, baseline BMD, but not prior bone loss, showed robust and reproducible association with incident dementia.

A meta-analysis is an effective approach to combine evidence across studies with similar study designs and comparable measures of outcomes, exposures, and covariates, although it is important to test for heterogeneity of results across studies.[21] In our study, the three studies designs were similar, and the measures were similar, except for skeletal site and type of BMD assessment. However, despite this difference, BMD effect estimates were quite similar across studies, and tests of heterogeneity were not significant. An alternative approach is to perform a cross cohort analysis which allows for more detailed characterization of cohort-specific effects, but this requires individual data analysis across studies which was not possible with our data use limitations.

A pertinent question is what mechanisms may link low BMD and bone loss to risk of dementia. This association may be due to common risk factors[8] or shared pathological mechanisms. Estrogen exposure has been associated with cognitive decline[22,23] and bone health[10]

although estrogen use was not associated with incident dementia in FHS in this study (data not shown). Immunological factors may contribute to both bone loss[24] and dementia.[25] Finally, circulating bone-derived proteins and cells have been shown to influence AD progression and cognitive decline.[26–29] Our studies occurred during the introduction of modern osteoporosis drugs like alendronate (FDA-approved in 1999). While alendronate use may increase BMD, the effects on dementia risk are unknown. The strengths of this study are that it uses three high-quality longitudinal studies with a combined sample size of 4431 with carefully adjudicated assessment of dementia and AD and either longitudinal assessment of bone density using gold standard DXA scanning or a single assessment using quantitative heel ultrasound. The limitations are participants are mostly of European ancestry, limiting generalizability, and lack of inclusion of exercise as a potential confounder. In conclusion, our results indicate that BMD, but not prior bone loss, is a strong and independent predictor of incident dementia in cognitively intact adults.

AUTHOR CONTRIBUTIONS

Christine W. Lary conceived the study and developed the study design in consultation with Alexa Beiser, Sudha Seshadri, and Douglas P. Kiel. Data analysis for the study was performed by Meghan Gerety, Alexandra Hinton, Christine W. Lary, and Samuel Ghatan. The interpretation of results and discussion was contributed to by Archana Nagarajan, Clifford Rosen, Ryan D. Ross, David A. Bennett, Anita L. DeStefano, Mohammad A. Ikram, and Fernando Rivadeneira. Christine W. Lary drafted the manuscript, and all authors reviewed and approved of the final manuscript.

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CONFLICT OF INTEREST STATEMENT

DPK serves on scientific advisory boards for Pfizer and Solarea Bio, has received royalty payments from Wolters Kluwer for authoring a chapter in UpToDate on Falls, and received grant funding through a grant to his Institute by the Dairy Council, Amgen, and Radius Health. An earlier version of this work was presented at the ASBMR annual meeting in Austin, TX September 9–12, 2022, and has been submitted as an abstract to the 8th Annual Skeletal Research Symposium on May 8th, 2023 in Boston, MA.

DATA AVAILABILITY STATEMENT

MAP resources can be requested at www.radc.rush.edu. FHS data for this study was made available through approved data use agreement #5187.

SPONSOR'S ROLE

The sponsors had no role in the conduct of this research study.

ORCID

Christine W. Lary https://orcid.org/0000-0001-5399-9602

Meghan Gerety https://orcid.org/0000-0002-8586-5139

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

Figure S1. Consort diagrams showing inclusion of the Framingham Heart Study (Original and Offspring) participants, Rotterdam Study (RS1) participants, and Memory and Aging Project participants.

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